

Working against the biological clock: a review for the Occupational Physician

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Abstract: The master clock of the biological rhythm, located in the suprachiasmatic nucleus of the anterior hypothalamus, synchronizes the molecular biological clock found in every cell of most peripheral tissues. The human circadian rhythm is largely based on the light-dark cycle. In night shift workers, alteration of the cycle and inversion of the sleep-wake rhythm can result in disruption of the biological clock and induce adverse health effects. This paper offers an overview of the main physiological mechanisms that regulate the circadian rhythm and of the health risks that are associated with its perturbation in shift and night workers. The Occupational Physician should screen shift and night workers for clinical symptoms related to the perturbation of the biological clock and consider preventive strategies to reduce the associated health risks.

Key words: Circadian rhythm, Biological clocks, Shift work schedule, Rotating shift work, Night shift work, Chronobiology disorders, Desynchronization of circadian rhythms, Health survey

Introduction

Life on Earth has adapted to the planet's 24-h rotation; the human biological rhythm is also circadian (Latin, *circa diem*). The 2017 Nobel Prize in Medicine and Physiology was awarded to Hall, Rosbash, and Young for their discoveries on the biological mechanisms that regulate the circadian clock. In the 1980s, they isolated in *Drosophila melanogaster* a gene (period) that regulates the daily biological rhythm. The gene encodes a protein (PER) that is produced during biological daytime and is subsequently degraded^{1, 2}.

In humans, nearly all cells of the body contains its own molecular circadian clock³. The entrainment of each of

these clocks to the 24-h day is based on the signal received from a master clock located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. The master clock consists of ca. 10,000 neurons and is itself synchronized to 24-h by information on environmental light received from intrinsically photosensitive retinal ganglion cells (ipRGCs) that are not involved in vision, which contain the photopigment melanopsin^{4, 5}. The function of the endogenous biological clock is to generate the circadian rhythms by entraining them to the external light-dark cycle. Accordingly, cortisol secretion and the rise in core body temperature take place in daytime, whereas melatonin secretion and sleep take place during the night⁶. These patterns occur when the circadian system is normally entrained to the 24-h light-dark cycle and are altered or not present in shift workers, those who travel across time zones, or in blind individual who have lost ipRGC signaling^{7, 8}.

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Functioning of the Biological Clock

The light-dark cycle is the main *zeitgeber* (German, time giver) acting on the SCN^{9, 10}. However, the circadian periodicity is ensured even in the absence of environmental light cues (free-running rhythm)^{11, 12}. The ability of the biological clock to generate self-sustaining rhythms relies on the presence in cells of genes called “clock genes” which generate an oscillation of the duration of about 24 h by transcription/translation feedback loops^{11, 13}. The main loop consists of two transcriptional activators, CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL (Brain and Muscle ARNT-Like protein), and the target genes period and cryptochrome, which code for the expression of their own protein products, respectively PER1, PER2, and PER3 and CRY1 and CRY2. Notably, CLOCK and BMAL1 accumulate in the cytoplasm and form CLOCK-BMAL1 heterodimers which translocate to the nucleus, where they bind the E-box sequences of period and cryptochrome genes, activating their expression. During the night, PER and CRY proteins accumulate in the cytoplasm and translocate to the nucleus, inhibiting the CLOCK-BMAL1 complex. In the early morning, their degradation by casein kinase suppresses the inhibition, enabling the resumption of CLOCK and BMAL1 transcription, and allowing a new cycle to begin. Another feedback loop regulates *bmal1* gene transcription *via* REV-ERB α and ROR α , which act respectively as a repressor and an activator^{13, 14}.

The clock genes are not localized exclusively to the SCN, but are also found in the cells of nearly all peripheral tissues (peripheral clock genes, PCGs), where they regulate the expression of several clock-controlled genes (CCGs)¹⁵.

Outputs of the Biological Clock

The main function of the biological clock is to regulate the circadian rhythms by integrating with other cerebral and extracerebral nervous centers, to ensure system homeostasis (Fig. 1). In humans there are two main circadian cycles, the sleep-wake and the hunger-satiety cycle, which are closely integrated because the awake phase coincides with feeding and the sleep phase coincides with satiety and fasting.

Central outputs: the sleep-wake cycle

The sleep-wake cycle is determined by a process that gauges the need for sleep as a proportion of the duration

of wake (process S) and by a circadian process (process C) that regulates the temporal distribution of wake and sleep independently of the duration of wake. Sleep in process S is ensured by “time windows” of sleep propensity between 9:30 p.m. and 11:30 p.m. (main window) and between 2 p.m. and 4 p.m. (secondary window)¹⁶. This rhythm of sleep propensity is ensured by the reciprocal transmission of data and information between the SCN and extra-SCN regions that play important roles in circadian control^{17–22}:

- hypothalamic nuclei in the lateral area (LHA) which produce orexin, a neuropeptide that is critical for the wake phase²³,
- nuclei making up the ascending reticular formation between the midbrain and the medulla oblongata, which also participate in wake and alertness²⁴,
- the dorsomedial hypothalamic nucleus, which through the ventrolateral preoptic nucleus regulates the sleep phase^{18, 25}.

The SCN exchanges information with the hypothalamic-pituitary-adrenal (HPA) axis and regulates the circadian expression patterns of cortisol²⁶, thyroid-stimulating hormone, somatotrophic hormone, and other hormones²⁷ through the paraventricular hypothalamic nucleus (PVN). Finally, its anatomical and functional relationship with the pineal gland allows the SCN to regulate its circadian melatonin production²⁸.

Box 1. Assessment of the clinical symptoms related to sleep-wake cycle perturbation

When assigning night shifts:

- workers should be assessed for chronic sleep disturbances being treated with hypnotics, anxiolytics, or antidepressants,
- night workers should be assessed for excessive daytime sleepiness due to lack of sleep.

Diagnostic tests include **polysomnography**^{29, 30} or **actigraphy**^{31–33} and psychometric tests such as:

- the **Stanford Sleepiness Scale**³⁴, which is commonly used to evaluate short-term changes in sleepiness;
- the **Leeds Sleep Evaluation Questionnaire**³⁵, which has been developed specifically to assess the effects on sleep of psychoactive drugs in general and of sedative hypnotic agents in particular;
- the **Sleep Disorders Questionnaire**³⁶, to diagnose sleep disturbances and their severity in the previous six months;
- the **Pittsburgh Sleep Quality Index**³⁷, a self-rating scale developed to provide a reliable, sound and

standardized measure of sleep quality. This tool distinguishes between “good” and “bad” sleepers and has clinical use in evaluating the different aspects of sleep that can compromise rest;

- the **Epworth Sleepiness Scale**³⁸⁾, which measures the level of daytime sleepiness.

Assessment of the circadian rhythm type (or chronotype) is important for clinicians. The **Morningness Eveningness Questionnaire**³⁹⁾ is the most widely used self-rating tool to establish the circadian type of adults.

zeitgeber role has been advanced for food nutrients, which would provide a sort of input to the peripheral clocks: some researchers have suggested the existence of a “food-entrainable oscillator” residing in the brain, whereas others hold that it is an integral part of the biological clock found in the SCN^{40, 41)}.

A third loop, characterized by activation of the gene *nampt* by the CLOCK-BMAL1 complex, has recently been described in the biological clock⁴²⁻⁴⁴⁾. *Nampt* controls the biosynthesis of nicotinamide adenine dinucleotide (NAD⁺), which in turn regulates the activity of the protein sirtuin 1 (SIRT1), which affects clock and *bmal1* transcription. NAD⁺ and SIRT1, together with AMPK (activated protein kinase), act as metabolic sensors, gauging cellular energy and nutrient requirements and sending their signals to the

Central outputs: the hunger-satiety cycle

Humans eat their meals at regular that characterize the daily schedules of organizations and families alike. A

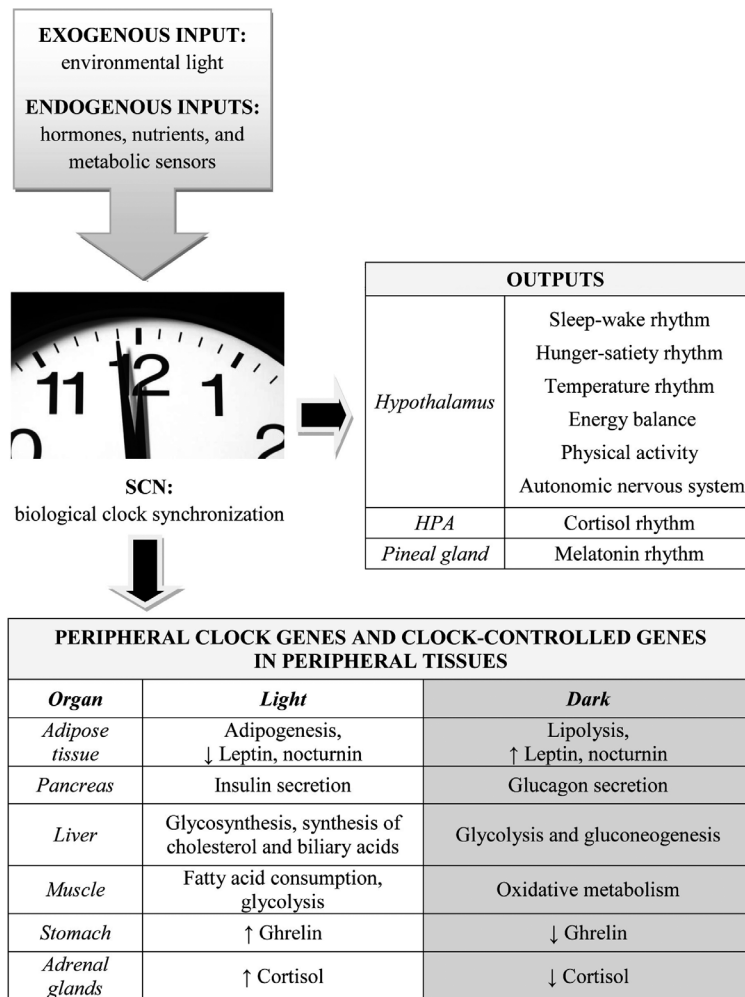


Fig. 1. The suprachiasmatic nucleus (SCN) receives exogenous environmental luminosity information through the retinohypothalamic tract as well as endogenous information from hormones (insulin, ghrelin, leptin), nutrients (amino acids, glucose, fatty acids) and metabolic sensors (NAD⁺/SIRT1/AMPK). The SCN provides several outputs from the hypothalamic nuclei, HPA axis, and pineal gland. It also regulates metabolism, energy expenditure, and hormones in peripheral tissues through hierarchical control of peripheral clock genes and clock-controlled genes.

SCN through the hypothalamic arcuate nucleus (ARC)⁴⁵, to anticipate energy and nutrient depletion⁴⁶.

During the night the increase of leptin induces an anorexigenic action deactivating neurons that synthesize anorexigenic neuropeptides. Leptin also suppresses melanocyte concentrating hormone, an anorexigenic hormone produced by LHA hypothalamic nuclei⁴⁰. Conversely, the morning ebb of leptin secretion results in immediate activation of the neurons producing the orexigenic neuropeptides⁴⁵.

Further mechanisms are involved in feeding patterns besides leptin signaling:

- the PVN, which is anatomically and functionally related with the ARC and the SCN, is responsible for the central control of feeding requirements through the measurement of the energy used by muscle activity¹⁸; it also regulates metabolic and energy activity in peripheral tissues through its direct connection to the autonomic nervous system^{47, 48} and controls HPA axis activity *via* direct innervation²⁷,
- the ventromedial hypothalamic nucleus is also connected to the ARC and regulates food intake and glycemic homeostasis⁴⁸.

Box 2. Assessment of the clinical symptoms related to hunger-satiety cycle perturbation

The possible effects of hunger-satiety cycle perturbation in shift workers is related to the interaction of two factors^{49–51}:

- changes in meal times
- the hunger experienced during night shifts, which leads to food intake.

Qualitative and quantitative information on the eating habits of shift workers can be collected by direct interviews or through a food diary⁵². Deviations from healthy eating can be corrected by formulating diets appropriate to the shift work or by asking companies to provide healthier food in canteens and vending machines^{53–55}.

Unhealthy eating habits can promote overweight, obesity, and cardiovascular diseases (CVDs) like type 2 diabetes (T2D), dyslipidemia, metabolic syndrome (MS) and myocardial infarction, and further affect the poor sleep patterns of shift workers^{56, 57}.

Central outputs: metabolic and energy control

The information reviewed above highlights the important role played by the SCN, LHA, and ARC in controlling food intake and sleep-wake patterns. The ARC integrates

short- and long-term hunger and satiety signals⁴⁵. The expression of metabolic hormone receptors (*e.g.* insulin, leptin, and ghrelin) is peripheral information sensed by the ARC and relayed to the central nervous system (CNS). Signals from nutrients and energy sensors (NAD⁺, SIRT1, and AMPK), located in peripheral cells and controlled by clock genes, trigger the demand for food and indicate which processes affecting the energy balance should be activated^{40, 45, 47, 48}. The circadian alignment of food intake and physical activity is essential for the control of body weight^{11, 58}. The orexin neurons in the LHA are involved both in alertness and in glucose metabolism²³.

Box 3. Assessment of the clinical symptoms related to perturbation of metabolic and energy control

Metabolic control can be adversely affected by night work and can promote conditions such as overweight and obesity, T2D, dyslipidemia and MS. Periodic assessment of parameters such as weight, abdominal circumference, body mass index (BMI), fasting glycemia, glycosylated hemoglobin, triglycerides and total, HDL and LDL cholesterol enables swift balance restoration in case of pathological changes^{56, 59, 60}.

The amount of energy used by basal metabolism and physical activity can change in individuals with poor eating habits, especially if they are associated with a sedentary lifestyle, as described in shift workers^{61, 62}. Energy use and other parameters (*e.g.* sleep duration) can be monitored by a metabolic Holter monitor worn for a few days^{63, 64}.

Central outputs: core body temperature

The SCN is connected to the medial preoptic region, where the centers that control core body temperature ensure the equilibrium of heat production and dissipation⁶⁵. Core body temperature also oscillates according to a circadian rhythm in relation to environmental light⁶⁶. Its trend subsumes all cortisol-activated ergotropic functions, including metabolic activity; values tend to rise in the morning, they peak at 4–5 p.m., and decline again, especially during the biological night, with a trough at 2–5 a.m. that ensures adequate night rest^{65, 66}. The nighttime temperature reduction is due to a greater peripheral heat dissipation through the skin and to a low metabolic rate, related to reduced energy requirements^{65, 67}.

Central outputs: hormone secretion

The SCN is connected to the pineal gland through the

sympathetic nervous system. Light inhibits signal transmission to the gland, hence melatonin production, until the night, when it peaks around 2–4 a.m.⁶⁸). Melatonin has been defined as a key that opens the doors to sleep^{16, 69}). It is involved in a number of cell functions, exerting antioxidant, antiestrogenic and immunomodulatory activities^{28, 70, 71}). The wake state coincides with HPA axis activation by the SCN and production of the ergotropic hormone cortisol²⁷). The SCN controls, *via* the PVN, the secretion of corticotropin releasing hormone, which acts on the pituitary by inducing the release of adrenocorticotrophic hormone (ACTH)²⁶); in turn, ACTH stimulates the adrenal cortex, where PCGs control cortisol production⁷²). Cortisol secretion peaks at 6–8 a.m. and declines during the evening and night. Insulin, produced by the pancreas, reaches a postprandial acrophase 60 min after meals, then declines. Blood glucose and insulin show SCN-dependent circadian oscillations, insulin reaching its acrophase around 5 p.m.⁴⁰), CCGs in the pancreas regulate insulin production⁷³). Leptin, which is also produced according to a circadian rhythm in white adipose tissue⁷⁴), exhibits low levels during the day and high nocturnal levels (acrophase around 1 a.m.). Leptin is also involved in the sleep-wake cycle, since sleep restriction induces leptin reduction^{75, 76}).

Peripheral outputs: peripheral clock genes

Although the function of PCGs is still largely unclear, they are likely to have a role in guiding the local rhythms of each tissue¹⁵). PCGs are hierarchically subordinated to the SCN and synchronized with its rhythm⁴⁶). However, they have been demonstrated to have also an autonomous rhythm, as they respond to local, tissue-specific requirements with local outputs (Fig. 1) that modulate the metabolic activity of pancreas, liver, muscle, and adipose tissue according to a circadian pattern^{40, 77, 78}). Studies that decoupled the meal timing cycle from the light-dark cycle showed that some PCGs respond more to food than to light^{79, 80}). PCGs in the liver participate in glucose metabolism according to a circadian rhythm^{81, 82}). PCGs in the pancreas (β -cell clock) are involved in the secretion of insulin; those located in the gut regulate nutrient adsorption; adipose tissue PCGs control fat accumulation through lipid synthesis, and muscle PCGs regulate glucose metabolism^{40, 48, 73, 83}).

Peripheral outputs: clock-controlled genes

CCGs, which are not capable of generating a self-sustaining circadian rhythm, are nonetheless expressed according to a circadian pattern through the hierarchical

control of the SCN. CCGs, like PCGs, are involved in the circadian regulation of several processes such as cell metabolism, the control of cellular DNA growth and damage, and the response to substances like xenobiotics, medications, and alcohol^{77, 84}). A CCG with an important role in cell metabolism is nocturnin (*NOC*), whose 24-h oscillation is under the control of the CLOCK-BMAL1 complex. Whereas most deadenylases are arrhythmic or have narrow rhythms that peak during the day, *NOC* shows high-amplitude rhythms with nocturnal peaks in mice⁸⁵). The *NOC* gene, though not belonging to the circadian clock, regulates the circadian cycles and adjusts them to the metabolic rhythms; since it is involved in lipid metabolism, adipogenesis, glucose homeostasis, and inflammation, it could have a role in promoting metabolic alterations^{86–88}). Mice whose gene has been silenced are resistant to obesity and hepatic steatosis, probably due to changes in lipid absorption by the gut or in their utilization in alternative metabolic cycles, simultaneously increasing glucose tolerance and insulin sensitivity⁸⁹).

The human genome is physiologically subject to damage caused by the products of normal metabolism (radicals, products of lipid peroxidation, alkylating agents), exogenous chemicals, and physical agents^{90, 91}). The worst damage is caused by reactive chemical species, which have been divided into those reactive to oxygen (ROS) and to nitrogen. Reactive chemical species induce DNA injury *via* oxidation, alkylation, nitration, and halogenation. The human organism can repair such damage in various ways. Base excision repair (BER) system identifies and removes 8-oxoguanine, the most widely investigated DNA oxidation lesion, which can induce DNA mutation^{90, 91}). According to a recent study by our group⁹¹), only *OGGI* of all BER system genes (*APEX1*, *XRCC1*, and *PARP1*) displays a circadian oscillation characterized by a peak at 8 a.m. and a trough at 8 p.m. Moreover, it correlates positively with period and cryptochrome and negatively with *BMAL1* and *REV-ERBa* mRNA levels. The repair activity of the enzyme OGG1 also follows a circadian oscillation pattern; as a result, *OGGI* downregulation during the night involves a slower night-time repair and enables DNA damage accumulation over time.

Box 4. Assessment of the circadian rhythms

The circadian rhythms can be assessed and any deviation identified by melatonin and cortisol dosage and by monitoring body temperature. Melatonin and cortisol can be measured in saliva, blood or urine^{92, 93}). The

major metabolite of melatonin is the 6-sulphatoxymelatonin, it can be measured in urine and is useful to assess the overnight production of melatonin⁹⁴). Body temperature data can be collected with metabolic Holters or small dataloggers. Body temperature measurement should be combined with the recording of physical activity using the metabolic Holter^{6, 95, 96}).

Peripheral clock gene and CCGs expression is a useful approach to circadian rhythm assessment and can be measured in various matrices (blood lymphocytes, hair bulb)^{6, 97, 98}).

Perturbation of the Biological Clock

Circadian rhythm changes are determined by discrepancies between the endogenous circadian rhythm and the exogenous rhythm, which cannot be compensated for by the biological clock. The misalignment of the sleep-wake cycle due to the exogenous rhythms imposed by life commitments result in fatigue, poor job performance, and sleep disturbances, especially difficulty in falling asleep or in waking at the desired hour. Jet lag, sleep disturbances, aging, and shift and night work are major causes of circadian rhythm disruption^{99–103}).

External perturbation: shift and night work

It is well established that shift and night work, its duration, and worker age affect the risk of developing some chronic disorders. Night work has been associated with abdominal adiposity, obesity, T2D, MS, CVD, cancer, and disturbed sleep^{59, 104–117}). Lack of sleep disrupts the circadian clock, disconnecting the environmental cycle (dark-light) from the biological cycle (sleep-wake). The chief consequence is a greater frequency of sleep disturbances in shift workers^{99, 118}), not only because they fail to rest during the biological night, but also because even shifts beginning at 6 a.m. prevent the completion of the last phase of sleep. Sleep restriction is associated with weight gain, which may be compounded by a sedentary lifestyle, and with abnormal ghrelin and leptin blood levels^{76, 119}), which can foster a greater food intake. Alterations in clock gene are associated with obesity and MS⁴⁸). The clock gene *bmal* is implicated in controlling adipogenesis and lipid metabolism in adipocytes¹²⁰), some variants are associated with a greater sensitivity to arterial hypertension and T2D¹²¹). Changes in *per2* gene expression are associated with obesity⁵⁸). NOC can also promote weight gain, since its higher levels during

the biological night stimulate fat absorption in the gut *via* chylomicrons⁸⁶). Sleep-wake cycle perturbation may foster nocturnin elevation, hence greater fat absorption by enterocytes, promoting the development of obesity and metabolic disturbances. *OGGI*-related DNA repair may also be affected, due to a slower removal of damaged bases. In a study by our group, nurses involved in shift work showed significant *OGGI* underexpression compared with day nurses⁹¹).

Exposure to artificial light during the night reduces melatonin secretion, which is quickly restored by a 24-h rest^{97, 122}). Body temperature is controlled by the medial preoptic region, which receives SCN outputs⁶⁵). Exposure to light affects thermoregulation⁶⁶): during the night, increased heat dissipation through the skin induces a reduction in core body temperature, whereas the more limited dissipation during the day raises it. Heat dissipation is also an important factor in the circadian regulation of core body temperature⁶⁵). Measurement of 24-h peripheral temperature found a significantly greater dissipation from 10 a.m. to 1 p.m. and from 8 to 10 p.m. in shift workers compared with day workers⁶), due to limited ergotropic activation associated with low cortisol values in the former and to an anticipation of the phase of sleep propensity in the latter. Desynchronization of the circadian rhythms has also been implicated in neoplastic disease (*e.g.* breast cancer) and CVD^{113, 114, 123–125}).

The demonstration of a cause-effect relationship between shift work and chronic disease is hampered by the non-univocal definition of shift and night work and by the need for long-term studies^{126, 127}). Moreover, a number of variables, like smoking habits, a high BMI, dietary habits, and sleep duration, affect results. Shift and night work duration and shift type are further, equally important variables. In 2007, the IARC defined shift work that induces circadian rhythm disruption as probably carcinogenic to humans (group 2A)¹¹³). In 2016, the National Toxicology Program (NTP) convened an expert panel at a public workshop entitled “Shift Work at Night, Artificial Light at Night, and Circadian Disruption” and conducted a literature-based health hazard assessment¹²⁸). Persistent night shift work that causes circadian disruption is now listed as “known to be a human carcinogen” in the draft of Report on Carcinogens Monograph on Night Shift Work and Light at Night¹²⁹).

Several experimental investigations have stressed that high melatonin production during the biological night is a powerful anticancer stimulus that can protect normal cells against the disease^{28, 69}). Its suppression due to night-time

exposure to artificial light has the potential to foster breast cancer development in night workers^{10, 112, 128, 130}), also in relation to higher β -estradiol levels detected in women shift workers⁹⁷). Other studies have found an association between night work and a greater CVD risk. A study of a population of more than 189,000 North-American shift woman nurses has found that greater job seniority in night work involves a greater risk of coronary heart disease. Specifically, in the younger cohort (mean age at baseline, 34.8 yr) a seniority of up to 5 yr involved a 12% higher risk, a seniority between 5 and 9 yr involved a 19% increase, and a seniority greater than 10 yr involved a 27% higher risk¹¹⁴).

Internal perturbation: aging

Shift and night workers who have been exposed to disruption of the circadian rhythms for years may experience accelerated aging and be at higher risk of disease. The biological clock undergoes a number of age-related changes, but whereas until recently they had been considered as part of the normal aging process, there is mounting evidence that circadian system dysfunctions can accelerate aging^{131, 132}). The adaptability of the biological clock declines with age. Sleep becomes increasingly fragmented, with frequent awakenings and a shortening of stages 3, 4 and REM sleep¹³³). Over the years the circadian rhythms tend to lose their temporal structure, while the oscillation amplitude of their outputs (core body temperature, melatonin and cortisol secretion) diminishes and shows phase advance¹³⁴). These changes are due less to the age-related reduction in CNS neurons than to changes in their properties, which include a reduction of resting membrane potential and transmission ability¹³⁵). In addition, aging is associated with a reduction in CNS dendritic spines and dendrite shortening, resulting in poorer neuron connectivity and synchronization with other neurons in the network, increasingly fragmented production of the circadian rhythm, and loss of rhythm amplitude¹³⁵).

Recent evidence shows that in subjects aged more than 60 yr the circadian oscillation of period genes in the brain shows decreased amplitude and a phase advance of 4–6 h, whereas *CRY1* expression becomes increasingly arrhythmic compared with individuals aged less than 40 yr¹³⁶). Neuropeptides VIP, AVP, and GABA, which play an important role in CNS cell rhythm synchronization, undergo an age-related reduced production that impairs CNS communication and synchronization abilities¹³⁴). Such changes are due partly to intrinsic

degeneration of the biological clock and partly to its altered responsiveness to environmental light. A study of human retina has shown that melanopsin-containing retinal ganglion cells, which mediate the synchronization of environmental light and CNS activity, diminish with age, reducing circadian rhythm outputs and giving rise to decreased oscillations and to phase advance¹³⁷). In *D. melanogaster* a number of genes called “late-life cyclers” (LLC), which are part of the circadian clock, undergo rhythmic activation in the final phases of life or at times of intense stress¹³⁸). LLC genes seem to be activated by and to respond to common age-related stimuli such as cellular and molecular damage, oxidative stress, and some pathological states. As age advances they become increasingly active, preventing the build-up of defective proteins; however, in a biological clock disrupted by chronic changes during the individual’s working life their action could be altered and actually induce an acceleration of aging.

Health Surveillance and Preventive Strategies

The Occupational Physician should assess shift workers for clinical symptoms related to the perturbation of the sleep-wake cycle, such as chronic sleep disturbance and excessive daytime drowsiness due to lack of sleep (Box 1). The sensation of hunger, experienced during night shifts, may induce changes in meal times that disturb the hunger-satiety cycle, resulting in overweight, obesity, type 2 diabetes, dyslipidemia, and metabolic syndrome (Box 2). Periodic assessment of parameters such as weight, abdominal circumference, body mass index (BMI), fasting glycemia, glycosylated hemoglobin, triglycerides and total, HDL and LDL cholesterol enables swift correction in case of pathological changes (Box 3). The assessment of specific parameters related to the biological clock like cortisol, melatonin, and body temperature and the expression of peripheral clock genes and CCGs is important in studies involving groups of workers; where individual workers are concerned, these tests may be prescribed for a higher level check-up (Box 4). With regard to the increasing evidence for an association between shift and night work and breast cancer, the Occupational Physician should suggest screening tests such as mammography^{139–141}). Screening mammography is generally recommended after the age of 50 yr, but it should be performed sooner (between 40 and 49 yr) in women who have often worked night shifts and have done so from an early age.

The Occupational Physician should also advise workers

on the strategies that can help limit the circadian desynchronization induced by shift work. Workers should try to preserve regular resting hours and avoid cutting the total number of hours of sleep, for instance by sleeping a few hours in the afternoon before a night shift and by going to bed earlier the evening before a morning shift. Meal times should be maintained as much as possible, taking the evening meal before the night shift. Exposure to intense light with a strong blue component before going to sleep should be avoided.

Shift work organization should follow some criteria that should be suggested to the employer^{142–145}. Fast rotation, i.e. limitation of the number of consecutive night shifts, and clockwise rotation should be preferred. Shifts should be at least 11 h apart. The morning shift should not begin too early, and shift duration should be commensurate to its difficulty. Work schedules should envisage a rest after a night shift and pauses during it. Ensuring the largest possible number of free Saturdays and Sundays would help preserve workers' social life and integration. Similarly, shifts should be scheduled in advance, they should be flexible, and workers should be able to exchange them.

Conclusions

Evidence continues to accumulate regarding the critical importance of circadian rhythms to health. This paper offers an overview of the physiological mechanisms regulating circadian processes and the health risks associated with disruption of rhythms. The Occupational Physician must take into careful consideration the circadian rhythms in research and clinical practice towards shift and night workers.

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